Mental Disorders, Stage of Cancer at Diagnosis and Subsequent Survival

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Complete List of Authors:	Chang, Chin-Kuo; King's College London, Institute of Psychiatry Hayes, Richard; Institute of Psychiatry, Kings College London, Psychological Medicine Broadbent, Matthew; South London and Maudsley NHS Fundation Trust, Hotopf, Matthew; King's College London (Institute of Psychiatry), Davies, Elizabeth; King's College London, Moller, Henrik; Kings College London, Thames Cancer Registry Stewart, Robert; King's College London, Institute of Psychiatry
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Mental Disorders, Stage of Cancer at Diagnosis and Subsequent Survival

Chin-Kuo Chang,[1]* Richard D Hayes,[1] Matthew TM Broadbent,[2] Matthew Hotopf,[1] Elizabeth Davies,[3] Henrik Møller,[3] Robert Stewart [1]

[1] King's College London (Institute of Psychiatry), London

[2] South London and Maudsley NHS Foundation Trust, London

[3] King's College London (Section of Cancer Epidemiology and Population Health), London

Corresponding Author: Dr. Chin-Kuo Chang, Box 63, King's College London (Institute of Psychiatry), De Crespigny Park, London SE5 8AF, United Kingdom. e-mail: chin-kuo.chang@kcl.ac.uk; TEL: +44 203 2288563; Fax: +44 203 2288551

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ABSTRACT

Background: There have been inconsistent research results reported for the effects of prior serious mental disorders on cancer mortality and morbidity.

Methods: Using the anonymised linkage between a regional monopoly secondary mental health service provider in southeast London and a population-based cancer register, a historical cohort study was constructed. Comparisons between people with and without specific psychiatric diagnosis in the same residence area for risks of advanced stage of cancer at diagnosis and general survival after cancer diagnosed were analysed using logistic and Cox models.

Results: A total of 28,477 cancer cases aged 15+ years old with stage of cancer recorded at diagnosis were identified. Among these, 2,206 subjects had been previously assessed or treated in secondary mental healthcare before their cancer diagnosis and 125 for severe mental illness (schizophrenia, schizoaffective, or bipolar disorders). No associations were found between specific mental disorder diagnoses and beyond-local spread of cancer at presentation. However, people with severe mental disorders, depression, dementia, and substance use disorders had significantly worse survival after cancer diagnosis, independent of cancer stage at diagnosis and other potential confounders.

Conclusions: Previous findings of associations between mental disorders and cancer mortality are more likely to be accounted for by differences in survival after cancer diagnosis rather than by delayed diagnosis.

Strengths and limitations of this study:

Main strengths:

- Longitudinal study design with a data linkage between two case register systems in London, UK
- Mortality information was retrieved from the national registry of death certificates in UK.

Limitations:

- The completeness rate of cancer stage was about 65%, which is within the range reported by other cancer registries in England and did not differ for most of the mental disorder groups of research interest compared to the remaining population.
- Lack of lifestyle factors (smoking, drinking, diet, obesity, and physical activities) for confounding control in survival analysis
- Small cancer case numbers of some specific mental disorders did not permit restricting the sample for sensitivity analyses. Also, size of the linked sample also did not allow further analyses of individual cancer diagnoses.

INTRODUCTION

Numerous studies have indicated a higher risk of all-cause mortality and shorter life expectancy for people with severe mental illness (SMI), including schizophrenia, bipolar disorder, schzoaffecive disorder, and sometimes depressive disorders.[1-8] The profile of causes of death among people with SMI is not substantially different from that in general population, although some specific patterns of death have been suggested, differing by sex, age group, and mental disorder diagnosis.[3 5-7 9-13] In recent decades, cardiovascular disease, stroke, respiratory diseases, suicide, and cancer have remained the leading causes.[3 5-7 9-13]

A recent population-based study revealed that men with psychiatric admissions before cancer registration had a significantly worse survival, especially for those with depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] Results from three population-based cohort studies showed significantly increased cancer mortality among people with schizophrenia for both genders,[5 9 15] but some other studies reported that it occurred in men[7 13 16 17] or women only.[18] However, other studies found no association with cancer mortality for SMI as a whole or schizophrenia specifically[7 13 16 17] and even a reduced risk was reported in one study.[6] Depression has also been found to be associated with an increase in cancer mortality.[19]

Studies of the incidence of cancer in people with SMI have principally focused on schizophrenia with varying results, including reduced total cancer incidence,[18 20-25] no difference,[26-29] or increased risk.[30] A meta-analysis pooling eight studies concluded no association between schizophrenia and incidence of cancer.[27] A history of depression or alcohol-related or substance use disorders has been associated with increased cancer,[31] but inconsistent findings have been found for bipolar disorder,[32 33] dementia,[15 18 34] and null for schizoaffective disorder.[29] Evidence on the role of mental disease as a comorbidity factor in cancer is therefore still far from conclusive, but tends to indicate cancer

incidence that is either reduced or not different, and cancer mortality that is increased.[32 33]

Thinking of how to solve the puzzle shown on conflicting research results and effects of mental disorders to cancer prognosis, there are two key research questions to be answered. First, to what extent might the reduced recognition of early cancer symptoms in people with mental disorders influence the stage of cancer at diagnosis?[33 35-37] And, secondly, what is the role of mental disorders on mortality after cancer diagnosis if the issue of later presentation of cancer could be ruled out? Then, an influence of mental disorders on cancer mortality in the absence of a clear effect on underlying risk could be explained by differences in treatment access, response and adherence, as previously raised by Kisely and colleagues.[15 38] Utilising a data linkage between a large secondary mental healthcare case register in southeast London and the regional cancer registry, we sought to investigate associations between mental disorder and both disease stage at cancer diagnosis and subsequent survival.

MATERIALS AND METHODS

The South London and Maudsley NHS Foundation Trust (SLAM) Biomedical Research Centre (BRC) Case Register

The SLAM BRC Case Register was used to provide data on mental disorders for the current study. SLAM is the near-monopoly provider of comprehensive secondary mental health services for a geographic catchment consisting of four London boroughs (Southwark, Lambeth, Lewisham, and Croydon) with approximately 1.23 million residents. Clients' records for all the services provided by SLAM were electronised in 2006. In 2008, the Clinical Record Interactive Search (CRIS) system was developed as a platform for investigators to search and access full but anonymised clinical data from the fully electronic health records system in SLAM for research purposes. All people receiving

SLAM care for psychiatric assessments and / or treatment were included in the database. The demographic characteristics and clinical profiles of the Case Register population have been fully described elsewhere.[39] Ethical approval as an anonymised data resource for secondary analyses was received from Oxfordshire REC C in 2008 (reference number 08/H0606/71).

Thames Cancer Registry (TCR)

At the time of the study, TCR was the largest of eight population-based cancer registries in England, covering a population of 12 million residents in London, Kent, Surry, and Sussex. Registration was initiated by pathology reports and clinical records from hospitals and information on death certificates received from the NHS Central Register through the Office of National Statistics in 1999. When cancer is recorded as the main or contributing cause of death in the Part 1 section, the certificate is routinely sent to the regional cancer registry. Further information on demographic, clinical details, and treatments received within the first six months after cancer diagnosis was retrieved from hospitals or hospital databases by trained data collection officers. A central regional database was maintained with data added continuously and robust data quality controls. To avoid double counting, information about new tumors was cross-checked against existing registered cases. Cancer registration and cancer surveillance take place in English registries under provisions of Section 251 of the Health and Social Care Act and this permission is reviewed annually. The Thames Cancer Registry was assessed to be more than 95% complete in 2001-2007 and considered as of sufficient quality for cancer outcomes analyses.[40 41]

Anonymised process of data linkage

Data from CRIS and TCR for residents in the SLAM geographic catchment were linked using an anonymisation process by the Health Research Support Service (HRSS) Pilot Programme which was

operated by the Department of Health as part of the NHS Research Capability Programme in the UK. Memoranda of Understanding were signed between SLAM and TCR through HRSS, which in turn designed and created an infrastructure to provide a safe and confidential platform for health research. With HRSS as the "trusted third party", the linkage was performed using a series of identifiers including the NHS number and was then irreversibly de-identified, replacing the NHS number with an encrypted HRSS identification (HRSS id). The initial sample selected for analysis comprised individuals on the TCR dataset within SLAM coverage area. Thus, a retrospective cohort study of people under the care of secondary mental health services could be performed.

Covariates included

Mental disorder diagnoses were identified from two sources within CRIS: i) a primary psychiatric diagnosis (Axis 1a) categorised by ICD-10 code (a structured field, compulsory for completion by services, with a specific date in the electronic clinical records system); and ii) a supplementary natural language processing application developed using General Architecture for Text Engineering (GATE) software which extracts text strings relating to a diagnosis statement in correspondence fields. The first diagnoses from either or both sources were then categorised into the following groupings (ICD codes): dementia (F00-03), substance use disorders (F10-19), schizophrenia (F20), schizoaffective disorder (F25), bipolar disorder (F31), depressive disorders (F32-33), anxiety disorders (F40-42), and personality disorders (F60-61). Severe mental illness (SMI) was defined as a diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or bipolar disorder (F31). In the TCR data, tumor stage at presentation of cancer was routinely extracted from an individual's medical records and categorised as follows: "local" (stage 1), "extension beyond the organ of origin" (stage 2), "regional lymph node involvement" (stage 3), and "metastasis" (stage 4). Cases without sufficient information about disease stage were classified as "not known". Date of cancer diagnosis, date of

birth, sex, type of cancer, primary care trust (geographic area), and ethnic group were also routinely collected in TCR and were used as covariates. In addition, the income domain of the index of multiple deprivations in 2007 was derived on the basis of the residential postcode.[42]

Statistical analysis

All the cancer cases diagnosed in the period from 1999 to 2008 in residents of the catchment area of four London boroughs under SLAM service coverage were included in current analyses. Through the linkage performed by HRSS, any cancer detected after a contact with SLAM was marked. If multiple tumors were registered in one person, only the first cancer onset was considered. Their primary psychiatric diagnosis given in SLAM services before the cancer was identified (if any) as the major exposure of interest in current analyses. Stage of disease at cancer diagnosis was categorised into two groups: i) early stage with no spread or only local extension beyond the organ of origin (localized stage), and ii) late stages with regional lymph node involvement or metastasis (advanced stage). This was treated as a binary dependent variable and was modeled against mental disorder diagnoses by logistic regressions. Cox regression models were then assembled to estimate associations between mental disorder and survival after cancer diagnosis. The duration of follow up was defined as the period from cancer diagnosis to the date of death (any cause) or the end of the follow-up period (12 Jun, 2010), provided by TCR. Age at cancer diagnosis, gender, type of cancer, year of cancer diagnosis, primary care trust (geographic area), ethnic groups, deprivation score for income, and stage at cancer diagnosis were treated as potential confounders, where appropriate. Area-level deprivation score for income was classified into quintiles, with the 1st quintile representing the most affluent areas and applied as the reference group in modeling. Stata/IC 12.1 software for Windows (Stata Corporation, 2011) was used for all the analyses.

RESULTS

The study sample

A total of 43,746 cancer cases were identified from TCR records. No significant associations were found between psychiatric diagnosis and missing stage data apart from a higher proportion of missing data in people with dementia (46.8%) compared to the remainder (35.0%). After the exclusion of people without confirmed cancer stage information and those younger than 15 years old at cancer diagnosis (n = 101), with missing date of birth (n = 1) or date of cancer diagnosis (n = 1), 28,477 cases (65.1%) remained and were included in our analyses. Among them, 55.3% were female. Up to the end of 2008, a total of 2,206 of these cancer cases had received any SLAM service (i.e. were present on the CRIS database), and 125 of these had received an SMI diagnosis prior to their cancer diagnosis.

Factors associated with extent of disease at cancer diagnosis

Of the analysed sample of cancer cases, 64.2% (n = 18,290) were diagnosed with localized stage of disease. Descriptive characteristics of the sample by stage at cancer diagnosis are presented in Table 1. Subjects with advanced stage of cancer at diagnosis were older and more likely to be male (both p values < .001), and there was significant variation by cancer type, year of diagnosis, primary care trust, and ethnic group (all p values < .001), although no clear linear trend for socio-economic deprivation was evident (details not shown).

Mental disorder and stage at cancer diagnosis

Associations between preceding mental disorders and stage at cancer diagnosis are summarised in Table 2. In summary, findings were null and there was no evidence of an association with any

diagnostic group after adjustment for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income.

Mental disorder and survival after cancer diagnosis

Associations between mental disorders and survival after cancer diagnosis are summarised in Table 3. SMI as a whole (and schizophrenia and schizoaffective disorder individually), depression, dementia, and substance use disorders were associated with worse survival after cancer diagnosis in fully adjusted models with relatively little attenuation following adjustment for stage at cancer diagnosis.

DISCUSSION

Main findings

This linkage between a population-based cancer register and a near-monopoly secondary mental health service provider with a geographic catchment of approximately 1.23 million residents provided a sufficiently large sample for this investigation. The key findings were that people who had been diagnosed with specific mental disorders in the secondary mental health service were not more likely to have cancer with advanced stage at diagnosis, but that many of the mental disorder groups had worse subsequent survival. This latter finding was significant for SMI as a whole, and for schizophrenia and schizoaffective disorder individually, as well as for those with diagnoses of depression, dementia, and substance use disorders prior to the cancer diagnosis. The stage of cancer at diagnosis in people with mental disorders did not explain their worse subsequent survival.

Advantages and limitations

The study described here benefited from the large size of the two data sources. The linkage allowed the longitudinal observation of a substantial number of cases with mental disorder diagnoses who had

subsequently developed cancer, and comparison group of the remaining people with cancer diagnoses from the same geographic catchment area. Ascertainment of vital status and deaths were achieved by linkage to death certificates provided electronically from the Office for National Statistics.

Limitations include a fairly large proportion with missing data on cancer stage (34.7%). This completeness level is within the range reported by other English registries and represents the data available to the registration process. These levels have been improving with the receipt of electronic pathology data from hospitals. Importantly, the proportions with missing stage data did not differ for most of the mental disorder groups of primary interest compared to the remaining population (the only exception being dementia) and principal findings are therefore unlikely to have been biased by availability of stage information. The other issue was the lack of lifestyle factors for smoking, drinking, diet, obesity, and physical activities in our dataset, which made further confounding control inapplicable. Another limitation was that some of the required data on mental disorders were drawn from years when there was less than full information, since electronic records became comprehensive across all SLAM services during 2006; however, case numbers did not permit restricting the sample any further for sensitivity analyses. The size of the linked sample also did not permit analyses of individual cancer diagnoses. Besides, the significant finding of schizoaffective disorder for survival after cancer diagnosis in Table 3 was based on 5 cases only.

Comparisons with related studies

In the relatively scarce literature about potentially delayed cancer diagnoses among people with mental disorders, the most recent published study reported a significantly higher proportion of metastasis at cancer presentation for psychiatric patients comparing to general population (7.1% versus 6.1%) in Western Australia, especially for the cancer of breast and lung.[15] A US study, linking Surveillance, Epidemiology and End Results data to Medicare, found that people without mental

disorder were slightly more likely to have an earlier detection of colon cancer than people who had any mental disorder (53.3% versus 49.7%), although it was partially contributed by higher proportion with unknown stage when colon cancer diagnosed (6.2% versus 14.6%). The frequency of diagnosis at autopsy for colon cancer among people without mental disorder was also significantly lower than cases (1.1% versus 4.4%).[35] However, these two studies did not adjust for potential confounders in their analyses, especially for type of cancer.[15 35] Another study focusing on breast cancer with confounders adjusted found that a history of major depression was associated with a delayed diagnosis of breast cancer representing an almost ten-fold increased risk, but the opposite direction of association was found for phobia.[43] Although we should have sufficient statistical power to identify the differences, our null findings for people undergoing assessment and treatment in secondary mental health services made the issue about delayed diagnosis of cancer among people with mental illness still inconclusive. Although potential explanation about specific psychological characteristics of dispositional insensitivity to threat (if the relation really exists) was found to be associated with delayed help seeking for symptoms of rectal cancer,[36] further in-depth investigations on the effect of mental disorders to physical healthcare utilisations is needed.

On the issue of survival for people with mental disorders after cancer diagnosis, a previous study of a population-based male Swedish cohort with psychiatric admissions before cancer diagnosis by registration found significantly worse survival, especially for those who had had depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] With a similar study design, Kisley *et al.* identified a significantly elevated risk of cancer mortality for people with psychiatric disorder in Canada.[38] Advanced analyses exploring the reasons for elevated all-cause mortality following cancer diagnosis were also reported for people with known mental disorders in Western Australia, finding reduced likelihood of surgery after diagnosis of colorectal,

breast, and cervical cancers in people with mental disorders and less radiotherapy or chemotherapy receipt.[15] The US linkage between Surveillance, Epidemiology and End Results data and Medicare found that receipt of colon cancer treatment (any treatment at all stages or chemotherapy at stage 3 only) was significantly lower for people with preexisting any mental disorder, mood disorder, psychiatric disorder, and dementia.[35] Our study provided additional support to the finding that, although the stage of diagnosis for cancer of people with mental illness was not more advanced, these people were still at higher risk of death comparing to their counterparts without mental illness. The underlying reasons might differ by medical care system in countries. Further details about the treatment trajectories after cancer diagnosis for people with mental disorder are needed for advanced studies.

Implications and direction for future studies

The wider question about cancer risk and outcome in people with mental disorders has received considerable attention over the years, although studies have principally investigated overall cancer-related mortality or cancer incidence. While findings about cancer screening uptake rates among people with SMI were inconsistent across and within countries,[44] one possible reason for reasonably consistent raised cancer-related mortality in people with mental disorders but inconsistent evidence for raised cancer incidence is that the mortality is explained by delays in presentation rather than increased risk. However, we found no evidence that prior mental disorder was associated with more advanced stage of cancer at diagnosis, a measure of delay in presentation, which might because that, in UK, since 2003, GPs have been incentivised under the guide of Quality and Outcomes Framework[45] to offer regular physical health reviews to people with long-term mental health problems, including preventative cancer screening appropriate to age and gender since 2006.

Instead, consistent with other findings,[14 15 35 38] we found an association with worse survival after cancer diagnosis that was not explained by stage at presentation. This suggests that effects of mental disorder on cancer mortality primarily exert themselves after the diagnosis. Causal pathways might include reduced access to medical treatment and care, differing decisions about or tolerance of intensive regimes, and the influence of other health problems or drug effects on survival. Also, there might be differences between cancers on the impact to survival for early diagnosis, but there were insufficient data to analyze such differences among types of cancer. Clearly the components of such disadvantage require further evaluation. A greater understanding is needed of levels of utilisation of healthcare services and potential barriers to this among people with mental illness, including the extent to which this is present across individual cancer diagnoses and to which it is accounted for by the specific symptoms of the mental disorders themselves, by accompanying social disadvantage, or potentially by stigma. Also worthy of further evaluation is the potential impact that mental healthcare could have on improving physical health and other indirect influences of mental disorders on adverse health outcomes.

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COMPETING INTERESTS

The authors declare no conflict of interest in this research.

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Table 1. Descriptive statistics of cancer patients in southeast London by stage at cancer presentation from 1999 to 2008

Variables	Number (%) / Mean ± SD		
		Subjects with stage at cancer diagnosis (N = 28,477)	
	All cases (N = 43,454)	Localized stage (n = 18,290)	Advanced stage (n = 10,187)
Age at cancer diagnosis (yrs)	63.31 ± 17.96	60.38 ± 19.15	66.80 ± 14.29
Gender			
Female	32,242 (53.49)	10,257 (56.08)	5,490 (53.89)
Male	20,212 (46.51)	8,033 (43.92)	4,697 (46.11)
Type of cancer			
Lung	5,286 (12.16)	1,724 (9.43)	2,068 (20.30)
Bladder	1,170 (2.69)	636 (3.48)	111 (1.09)
Breast	5,943 (13.68)	2,592 (14.17)	1,833 (17.99)
Skin	2,189 (5.04)	1,548 (8.46)	93 (0.91)
Prostate	4,975 (11.45)	2,657 (14.53)	634 (6.22)
Corpus Uteri	804 (1.85)	485 (2.65)	121 (1.19)
Colorectal	3,979 (9.16)	1,441 (7.88)	1,531 (15.03)
Others	19,108 (43.97)	7,207 (39.40)	3,796 (37.26)

Ethnicity			
White	26,055 (59.96)	10,766 (58.86)	6,797 (66.72)
Black	5,080 (11.69)	2,293 (12.54)	1,293 (12.69)
East Asian	541 (1.24)	222 (1.21)	135 (1.33)
South Asian	804 (1.85)	258 (1.41)	173 (1.70)
Others/Unknown/mixed	10,974 (25.25)	4,751 (25.98)	1,789 (17.56)
Deprivation score (income)			
1st quintile	2,465 (5.67)	709 (3.88)	417 (4.09)
2nd quintile	3,308 (7.61)	1,098 (6.00)	629 (6.17)
3rd quintile	6,520 (15.00)	2,844 (15.55)	1,355 (13.30)
4th quintile	14,114 (32.48)	6,130 (33.52)	3,308 (32.47)
5th quintile	17,047 (39.23)	7,509 (41.06)	4,478 (43.96)

Table 2. Associations between previous diagnosis received in secondary mental healthcare and stage at cancer diagnosis (N = 28,477)

	Cancer Stage at Diagnosis Number (%)			Age- and gender-adjusted	
Variables	Localized stage (n = 18,290)	Advanced stage (n = 10,187)	Unadjusted odds ratio for advanced cancer stage (95% CI)	odds ratio for advanced cancer stage (95% CI)	Fully adjusted odds ratio for advanced cancer stage [b] (95% CI)
Severe mental illness (SMI) [a]					
No	18,208 (64.22)	10,144 (35.78)	Ref	Ref	Ref
Yes	82 (65.60)	43 (34.40)	0.94 (0.65, 1.36)	1.01 (0.70, 1.47)	0.94 (0.64, 1.39)
Schizophrenia					

No	18,233 (64.24)	10,151 (35.76)	Ref	Ref	Ref
Yes	57 (61.29)	36 (38.71)	1.13 (0.75, 1.72)	1.23 (0.81, 1.88)	1.10 (0.71, 1.71)
Bipolar disorder					
No	18,266 (64.21)	10,180 (35.79)	Ref	Ref	Ref
Yes	24 (77.42)	7 (22.58)	0.52 (0.22, 1.22)	0.55 (0.24, 1.30)	0.60 (0.25, 1.42)
Schizoaffective disorder					
No	18,286 (64.22)	10,186 (357.8)	Ref	Ref	Ref
Yes	4 (80.0)	1 (20.0)	0.45 (0.05, 4.02)	0.47 (0.05, 4.38)	0.47 (0.04, 4.95)
Depression					
No	18,184 (64.22)	10,129 (35.78)	Ref	Ref	Ref
Yes	106 (64.63)	58 (36.37)	0.98 (0.71, 1.35)	0.91 (0.66, 1.26)	0.90 (0.64, 1.27)

Dementia					
No	18,229 (64.26)	10,137 (35.74)	Ref	Ref	Ref
Yes	61 (54.95)	50 (45.05)	1.47 (1.01, 2.14)*	1.00 (0.68, 1.46)	1.23 (0.82, 1.85)
Substance use disorders					
No	18,260 (64.23)	10,171 (35.77)	Ref	Ref	Ref
Yes	30 (65.22)	16 (34.78)	0.96 (0.52, 1.76)	1.01 (0.55, 1.87)	0.99 (0.52, 1.89)
Anxiety disorders					
No	18,263 (64.22)	10,173 (35.78)	Ref	Ref	Ref
Yes	27 (65.85)	14 (34.14)	0.93 (0.49, 1.78)	0.98 (0.51, 1.89)	1.15 (0.58, 2.28)
Personality disorders					
No	18,282 (64.24)	10,179 (35.76)	Ref	Ref	Ref

Yes	8 (50.00)	8 (50.00)	1.80 (0.67, 4.79)	2.15 (0.80, 5.76)	1.78 (0.65, 4.88)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Adjust for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

* Statistical significance

Table 3. Crude and adjusted relative risks for the effect of pre-existing mental disorders on general mortality among cancer patients in southeast London by Cox models (N = 43,449)

Variables	Hazard Ratio (95% Confidence Interval)		
	Age- and gender-adjusted	Model 1 [b]	Model 2 [c]
Serious Mental Illness (SMI) [a]			
No	Ref	Ref	Ref
Yes	1.53 (1.27, 1.85)*	1.71 (1.44, 2.06)*	1.74 (1.44, 2.10)*
Schizophrenia			
No	Ref	Ref	Ref
Yes	1.71 (1.38, 2.11)*	1.91 (1.55, 2.37)*	1.90 (1.54, 2.36)*
Bipolar disorder			

No	Ref	Ref	Ref
Yes	1.01 (0.66, 1.55)	1.13 (0.74, 1.73)	1.20 (0.78, 1.85)
Schizoaffective disorder			
No	Ref	Ref	Ref
Yes	3.22 (1.45, 7.17)*	2.69 (1.21, 5.98)*	2.33 (1.05, 5.20)*
Depression			
No	Ref	Ref	Ref
Yes	1.22 (1.04, 1.44)*	1.27 (1.07, 1.49)*	1.30 (1.11, 1.54)*
Dementia			
No	Ref	Ref	Ref
Yes	1.36 (1.17, 1.58)*	1.65 (1.42, 1.92)*	1.66 (1.43, 1.94)*

Substance use disorders			
No	Ref	Ref	Ref
Yes	1.24 (0.89, 1.72)	1.41 (1.02, 1.96)*	1.42 (1.02, 1.97)*
Anxiety disorders			
No	Ref	Ref	Ref
Yes	0.74 (0.50, 1.10)	0.86 (0.58, 1.30)	0.73 (0.49, 1.10)
Personality disorders			
No	Ref	Ref	Ref
Yes	1.65 (0.94, 2.91)	1.58 (0.90, 2.79)	1.50 (0.85, 2.64)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Model 1: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

[c] Model 2: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, deprivation score for income, and stage at cancer diagnosis

* Statistical significance

A Cohort Study on Mental Disorders, Stage of Cancer at Diagnosis and Subsequent Survival

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A Cohort Study on Mental Disorders, Stage of Cancer at Diagnosis and Subsequent Survival

Chin-Kuo Chang,[1]* Richard D Hayes,[1] Matthew TM Broadbent,[2] Matthew Hotopf,[1] Elizabeth Davies,[3] Henrik Møller,[3] Robert Stewart [1]

[1] King's College London (Institute of Psychiatry), London

[2] South London and Maudsley NHS Foundation Trust, London

[3] King's College London (Section of Cancer Epidemiology and Population Health), London

Corresponding Author: Dr. Chin-Kuo Chang, Box 92, King's College London (Institute of Psychiatry), De Crespigny Park, London SE5 8AF, United Kingdom. e-mail: chin-kuo.chang@kcl.ac.uk; TEL: +44 203 2288563; Fax: +44 203 2288551

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ABSTRACT

Background: There have been inconsistent research results reported for the effects of prior serious mental disorders on cancer mortality and morbidity.

Methods: Using the anonymised linkage between a regional monopoly secondary mental health service provider in southeast London and a population-based cancer register, a historical cohort study was constructed. Comparisons between people with and without specific psychiatric diagnosis in the same residence area for risks of advanced stage of cancer at diagnosis and general survival after cancer diagnosed were analysed using logistic and Cox models.

Results: A total of 28,477 cancer cases aged 15+ years old with stage of cancer recorded at diagnosis were identified. Among these, 2,206 subjects had been previously assessed or treated in secondary mental healthcare before their cancer diagnosis and 125 for severe mental illness (schizophrenia, schizoaffective, or bipolar disorders). No associations were found between specific mental disorder diagnoses and beyond-local spread of cancer at presentation. However, people with severe mental disorders, depression, dementia, and substance use disorders had significantly worse survival after cancer diagnosis, independent of cancer stage at diagnosis and other potential confounders.

Conclusions: Previous findings of associations between mental disorders and cancer mortality are more likely to be accounted for by differences in survival after cancer diagnosis rather than by delayed diagnosis.

Strengths and limitations of this study:

Main strengths:

- Longitudinal study design with a data linkage between two case register systems in London, UK
- Mortality information was retrieved from the national registry of death certificates in UK.

Limitations:

- The completeness rate of cancer stage was about 65%, which is within the range reported by other cancer registries in England and did not differ for most of the mental disorder groups of research interest compared to the remaining population.
- Lack of lifestyle factors (smoking, drinking, diet, obesity, and physical activities) for confounding control in survival analysis
- Small cancer case numbers of some specific mental disorders did not permit restricting the sample for sensitivity analyses. Also, size of the linked sample also did not allow further analyses of individual cancer diagnoses.

INTRODUCTION

Numerous studies have indicated a higher risk of all-cause mortality and shorter life expectancy for people with severe mental illness (SMI), including schizophrenia, bipolar disorder, schzoaffecive disorder, and sometimes depressive disorders.[1-8] The profile of causes of death among people with SMI is not substantially different from that in general population, although some specific patterns of death have been suggested, differing by sex, age group, and mental disorder diagnosis.[3 5-7 9-13] In recent decades, cardiovascular disease, stroke, respiratory diseases, suicide, and cancer have remained the leading causes.[3 5-7 9-13]

A recent population-based study revealed that men with psychiatric admissions before cancer registration had a significantly worse survival, especially for those with depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] Results from three population-based cohort studies showed significantly increased cancer mortality among people with schizophrenia for both genders,[5 9 15] but some other studies reported that it occurred in men[7 13 16 17] or women only.[18] However, other studies found no association with cancer mortality for SMI as a whole or schizophrenia specifically[7 13 16 17] and even a reduced risk was reported in one study.[6] Depression has also been found to be associated with an increase in cancer mortality.[18] Studies of the incidence of cancer in people with SMI have principally focused on schizophrenia with varying results, including reduced total cancer incidence,[19 20-25] no difference,[26-29] or increased risk.[30] A meta-analysis pooling eight studies concluded no association between schizophrenia and incidence of cancer.[27] A history of depression or alcohol-related or substance use disorders has been associated with increased cancer,[31] but inconsistent findings have been found for bipolar disorder,[32 33] dementia,[15 18 34] and null for schizoaffective disorder.[29] Evidence on the role of mental disease as a comorbidity factor in cancer is therefore still far from conclusive, but tends to indicate cancer

incidence that is either reduced or not different, and cancer mortality that is increased.[32 33]

Thinking of how to solve the puzzle shown on conflicting research results and effects of mental disorders to cancer prognosis, there are two key research questions to be answered. First, to what extent might the reduced recognition of early cancer symptoms in people with mental disorders influence the stage of cancer at diagnosis?[33 35-37] And, secondly, what is the role of mental disorders on mortality after cancer diagnosis if the issue of later presentation of cancer could be ruled out? Then, an influence of mental disorders on cancer mortality in the absence of a clear effect on underlying risk could be explained by differences in treatment access, response and adherence, as previously raised by Kisely and colleagues.[15 38] Utilising a data linkage between a large secondary mental healthcare case register in southeast London and the regional cancer registry, we sought to investigate associations between mental disorder and both disease stage at cancer diagnosis and subsequent survival.

MATERIALS AND METHODS

The South London and Maudsley NHS Foundation Trust (SLAM) Biomedical Research Centre (BRC) Case Register

The SLAM BRC Case Register was used to provide data on mental disorders for the current study. SLAM is the near-monopoly provider of comprehensive secondary mental health services for a geographic catchment consisting of four London boroughs (Southwark, Lambeth, Lewisham, and Croydon) with approximately 1.23 million residents. Clients' records for all the services provided by SLAM were electronised in 2006. In 2008, the Clinical Record Interactive Search (CRIS) system was developed as a platform for investigators to search and access full but anonymised clinical data from the fully electronic health records system in SLAM for research purposes. All people receiving

SLAM care for psychiatric assessments and / or treatment were included in the database. The demographic characteristics and clinical profiles of the Case Register population have been fully described elsewhere.[39] Ethical approval as an anonymised data resource for secondary analyses was received from Oxfordshire REC C in 2008 (reference number 08/H0606/71).

Thames Cancer Registry (TCR)

At the time of the study, TCR was the largest of eight population-based cancer registries in England, covering a population of 12 million residents in London, Kent, Surry, and Sussex. Registration was initiated by pathology reports and clinical records from hospitals and information on death certificates received from the NHS Central Register through the Office of National Statistics in 1999. When cancer is recorded as the main or contributing cause of death in the Part 1 section, the certificate is routinely sent to the regional cancer registry. Further information on demographic, clinical details, and treatments received within the first six months after cancer diagnosis was retrieved from hospitals or hospital databases by trained data collection officers. A central regional database was maintained with data added continuously and robust data quality controls. To avoid double counting, information about new tumors was cross-checked against existing registered cases. Cancer registration and cancer surveillance take place in English registries under provisions of Section 251 of the Health and Social Care Act and this permission is reviewed annually. The Thames Cancer Registry was assessed to be more than 95% complete in 2001-2007 and considered as of sufficient quality for cancer outcomes analyses.[40 41]

Anonymised process of data linkage

Data from CRIS and TCR for residents in the SLAM geographic catchment were linked using an anonymisation process by the Health Research Support Service (HRSS) Pilot Programme which was

operated by the Department of Health as part of the NHS Research Capability Programme in the UK. Memoranda of Understanding were signed between SLAM and TCR through HRSS, which in turn designed and created an infrastructure to provide a safe and confidential platform for health research. With HRSS as the "trusted third party", the linkage was performed using a series of identifiers including the NHS number and was then irreversibly de-identified, replacing the NHS number with an encrypted HRSS identification (HRSS id). The initial sample selected for analysis comprised individuals on the TCR dataset within SLAM coverage area. Thus, a retrospective cohort study of people under the care of secondary mental health services could be performed.

Covariates included

Mental disorder diagnoses were identified from two sources within CRIS: i) a primary psychiatric diagnosis (Axis 1a) categorised by ICD-10 code (a structured field, compulsory for completion by services, with a specific date in the electronic clinical records system); and ii) a supplementary natural language processing application developed using General Architecture for Text Engineering (GATE) software which extracts text strings relating to a diagnosis statement in correspondence fields. The first diagnoses from either or both sources were then categorised into the following groupings (ICD codes): dementia (F00-03), substance use disorders (F10-19), schizophrenia (F20), schizoaffective disorder (F25), bipolar disorder (F31), depressive disorders (F32-33), anxiety disorders (F40-42), and personality disorders (F60-61). Severe mental illness (SMI) was defined as a diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or bipolar disorder (F31). In the TCR data, tumor stage at presentation of cancer was routinely extracted from an individual's medical records and categorised as follows: "local" (stage 1), "extension beyond the organ of origin" (stage 2), "regional lymph node involvement" (stage 3), and "metastasis" (stage 4). Cases without sufficient information about disease stage were classified as "not known". Date of cancer diagnosis, date of

birth, sex, type of cancer, primary care trust (geographic area), and ethnic group were also routinely collected in TCR and were used as covariates. In addition, the income domain of the index of multiple deprivations in 2007 was derived on the basis of the residential postcode.[42]

Statistical analysis

All the cancer cases diagnosed in the period from 1999 to 2008 in residents of the catchment area of four London boroughs under SLAM service coverage were included in current analyses. Through the linkage performed by HRSS, any cancer detected after a contact with SLAM was marked. If multiple tumors were registered in one person, only the first cancer onset was considered. Their primary psychiatric diagnosis given in SLAM services before the cancer was identified (if any) as the major exposure of interest in current analyses. Stage of disease at cancer diagnosis was categorised into two groups: i) early stage with no spread or only local extension beyond the organ of origin (localized stage), and ii) late stages with regional lymph node involvement or metastasis (advanced stage). This was treated as a binary dependent variable and was modeled against mental disorder diagnoses by logistic regressions. Cox regression models were then assembled to estimate associations between mental disorder and survival after cancer diagnosis. The duration of follow up was defined as the period from cancer diagnosis to the date of death (any cause) or the end of the follow-up period (12 Jun, 2010), provided by TCR. Age at cancer diagnosis, gender, type of cancer, year of cancer diagnosis, primary care trust (geographic area), ethnic groups, deprivation score for income, and stage at cancer diagnosis were treated as potential confounders, where appropriate. Area-level deprivation score for income was classified into quintiles, with the 1st quintile representing the most affluent areas and applied as the reference group in modeling. Stata/IC 12.1 software for Windows (Stata Corporation, 2011) was used for all the analyses.

RESULTS

The study sample

A total of 43,746 cancer cases were identified from TCR records. Among them, 15,166 subjects (34.7%) had no information about their stage of cancer at diagnosis. No significant associations were found between psychiatric diagnosis and missing cancer stage data apart from a higher proportion of missing data in people with dementia (46.8%) compared to the remainder (35.0%). After the exclusion of people without confirmed cancer stage information and those younger than 15 years old at cancer diagnosis (n = 101), with missing date of birth (n = 1) or date of cancer diagnosis (n = 1), 28,477 cases (65.1%) remained and were included in our analyses. Among them, 55.3% were female. Up to the end of 2008, a total of 2,206 of these cancer cases had received any SLAM service (i.e. were present on the CRIS database), and 125 of these had received an SMI diagnosis prior to their cancer diagnosis.

Factors associated with extent of disease at cancer diagnosis

Of the analysed sample of cancer cases, 64.2% (n = 18,290) were diagnosed with localized stage of disease. Descriptive characteristics of the sample by stage at cancer diagnosis are presented in Table 1. Subjects with advanced stage of cancer at diagnosis were older and more likely to be male (both p values < .001), and there was significant variation by cancer type, year of diagnosis, primary care trust, and ethnic group (all p values < .001), although no clear linear trend for socio-economic deprivation was evident (details not shown).

Mental disorder and stage at cancer diagnosis

Associations between preceding mental disorders and stage at cancer diagnosis are summarised in Table 2. In summary, findings were null and there was no evidence of an association with any

diagnostic group after adjustment for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income.

Mental disorder and survival after cancer diagnosis

Associations between mental disorders and survival after cancer diagnosis are summarised in Table 3. SMI as a whole (and schizophrenia and schizoaffective disorder individually), depression, dementia, and substance use disorders were associated with worse survival after cancer diagnosis in fully adjusted models with relatively little attenuation following adjustment for stage at cancer diagnosis.

DISCUSSION

Main findings

This linkage between a population-based cancer register and a near-monopoly secondary mental health service provider with a geographic catchment of approximately 1.23 million residents provided a sufficiently large sample for this investigation. The key findings were that people who had been diagnosed with specific mental disorders in the secondary mental health service were not more likely to have cancer with advanced stage at diagnosis, but that many of the mental disorder groups had worse subsequent survival. This latter finding was significant for SMI as a whole, and for schizophrenia and schizoaffective disorder individually, as well as for those with diagnoses of depression, dementia, and substance use disorders prior to the cancer diagnosis. The stage of cancer at diagnosis in people with mental disorders did not explain their worse subsequent survival.

Advantages and limitations

The study described here benefited from the large size of the two data sources. The linkage allowed the longitudinal observation of a substantial number of cases with mental disorder diagnoses who had

subsequently developed cancer, and comparison group of the remaining people with cancer diagnoses from the same geographic catchment area. Ascertainment of vital status and deaths were achieved by linkage to death certificates provided electronically from the Office for National Statistics.

Limitations include a fairly large proportion with missing data on cancer stage (34.7%). This completeness level is within the range reported by other English registries and represents the data available to the registration process. These levels have been improving with the receipt of electronic pathology data from hospitals. Importantly, the proportions with missing stage data did not differ for most of the mental disorder groups of primary interest compared to the remaining population (the only exception being dementia) and principal findings are therefore unlikely to have been biased by availability of stage information. The other issue was the lack of lifestyle factors for smoking, drinking, diet, obesity, and physical activities in our dataset, which made further confounding control inapplicable. Another limitation was that some of the required data on mental disorders were drawn from years when there was less than full information, since electronic records became comprehensive across all SLAM services during 2006; however, case numbers did not permit restricting the sample any further for sensitivity analyses. The size of the linked sample also did not permit analyses of individual cancer diagnoses. Besides, the significant finding of schizoaffective disorder for survival after cancer diagnosis in Table 3 was based on 5 cases only.

Comparisons with related studies

In the relatively scarce literature about potentially delayed cancer diagnoses among people with mental disorders, the most recent published study reported a significantly higher proportion of metastasis at cancer presentation for psychiatric patients comparing to general population (7.1% versus 6.1%) in Western Australia, especially for the cancer of breast and lung.[15] A US study, linking Surveillance, Epidemiology and End Results data to Medicare, found that people without mental

disorder were slightly more likely to have an earlier detection of colon cancer than people who had any mental disorder (53.3% versus 49.7%), although it was partially contributed by higher proportion with unknown stage when colon cancer diagnosed (6.2% versus 14.6%). The frequency of diagnosis at autopsy for colon cancer among people without mental disorder was also significantly lower than cases (1.1% versus 4.4%).[35] However, these two studies did not adjust for potential confounders in their analyses, especially for type of cancer.[15 35] Another study focusing on breast cancer with confounders adjusted found that a history of major depression was associated with a delayed diagnosis of breast cancer representing an almost ten-fold increased risk, but the opposite direction of association was found for phobia.[43] Although we should have sufficient statistical power to identify the differences, our null findings for people undergoing assessment and treatment in secondary mental health services made the issue about delayed diagnosis of cancer among people with mental illness still inconclusive. Although potential explanation about specific psychological characteristics of dispositional insensitivity to threat (if the relation really exists) was found to be associated with delayed help seeking for symptoms of rectal cancer,[36] further in-depth investigations on the effect of mental disorders to physical healthcare utilisations is needed.

On the issue of survival for people with mental disorders after cancer diagnosis, a previous study of a population-based male Swedish cohort with psychiatric admissions before cancer diagnosis by registration found significantly worse survival, especially for those who had had depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] With a similar study design, Kisley *et al.* identified a significantly elevated risk of cancer mortality for people with psychiatric disorder in Canada.[38] Advanced analyses exploring the reasons for elevated all-cause mortality following cancer diagnosis were also reported for people with known mental disorders in Western Australia, finding reduced likelihood of surgery after diagnosis of colorectal,

breast, and cervical cancers in people with mental disorders and less radiotherapy or chemotherapy receipt.[15] The US linkage between Surveillance, Epidemiology and End Results data and Medicare found that receipt of colon cancer treatment (any treatment at all stages or chemotherapy at stage 3 only) was significantly lower for people with preexisting any mental disorder, mood disorder, psychiatric disorder, and dementia.[35] Our study provided additional support to the finding that, although the stage of diagnosis for cancer of people with mental illness was not more advanced, these people were still at higher risk of death comparing to their counterparts without mental illness. The underlying reasons might differ by medical care system in countries. Further details about the treatment trajectories after cancer diagnosis for people with mental disorder are needed for advanced studies.

Implications and direction for future studies

The wider question about cancer risk and outcome in people with mental disorders has received considerable attention over the years, although studies have principally investigated overall cancer-related mortality or cancer incidence. While findings about cancer screening uptake rates among people with SMI were inconsistent across and within countries,[44] one possible reason for reasonably consistent raised cancer-related mortality in people with mental disorders but inconsistent evidence for raised cancer incidence is that the mortality is explained by delays in presentation rather than increased risk. However, we found no evidence that prior mental disorder was associated with more advanced stage of cancer at diagnosis, a measure of delay in presentation, which might because that, in UK, since 2003, GPs have been incentivised under the guide of Quality and Outcomes Framework[45] to offer regular physical health reviews to people with long-term mental health problems, including preventative cancer screening appropriate to age and gender since 2006.

Instead, consistent with other findings,[14 15 35 38] we found an association with worse survival after cancer diagnosis that was not explained by stage at presentation. This suggests that effects of mental disorder on cancer mortality primarily exert themselves after the diagnosis. Causal pathways might include reduced access to medical treatment and care, differing decisions about or tolerance of intensive regimes, and the influence of other health problems or drug effects on survival. Also, there might be differences between cancers on the impact to survival for early diagnosis, but there were insufficient data to analyze such differences among types of cancer. Clearly the components of such disadvantage require further evaluation. A greater understanding is needed of levels of utilisation of healthcare services and potential barriers to this among people with mental illness, including the extent to which this is present across individual cancer diagnoses and to which it is accounted for by the specific symptoms of the mental disorders themselves, by accompanying social disadvantage, or potentially by stigma. Also worthy of further evaluation is the potential impact that mental healthcare could have on improving physical health and other indirect influences of mental disorders on adverse health outcomes.

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COMPETING INTERESTS

The authors declare no conflict of interest in this research.

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CONTRIBUTORSHIP

Everyone listed as an author fulfils all three of the ICMJE guidelines for authorship, including 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published.

DATA SHARING

We declare that we are willing to share our data for the purpose of collaborations to investigators in related academic fields.

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Table 1. Descriptive statistics of cancer patients in southeast London by stage at cancer presentation from 1999 to 2008

	Number (%) / Mean ± SD			
		Subjects with stage at cancer diagnosis (N = 28,477)		
Variables	All cases (N = 43,454) [a]	Localized stage (n = 18,290)	Advanced stage (n = 10,187)	p-value [b]
Age at cancer diagnosis (yrs)	63.31 ± 17.96	60.38 ± 19.15	66.80 ± 14.29	<0.01*
Gender				
Female	23,242 (53.49)	10,257 (56.08)	5,490 (53.89)	<0.01*
Male	20,212 (46.51)	8,033 (43.92)	4,697 (46.11)	
Type of cancer				
Lung	5,286 (12.16)	1,724 (9.43)	2,068 (20.30)	
Bladder	1,170 (2.69)	636 (3.48)	111 (1.09)	
Breast	5,943 (13.68)	2,592 (14.17)	1,833 (17.99)	
Skin	2,189 (5.04)	1,548 (8.46)	93 (0.91)	<0.01*
Prostate	4,975 (11.45)	2,657 (14.53)	634 (6.22)	
Corpus Uteri	804 (1.85)	485 (2.65)	121 (1.19)	
Colorectal	3,979 (9.16)	1,441 (7.88)	1,531 (15.03)	
Others	19,108 (43.97)	7,207 (39.40)	3,796 (37.26)	

Ethnicity				
White	26,055 (59.96)	10,766 (58.86)	6,797 (66.72)	
Black	5,080 (11.69)	2,293 (12.54)	1,293 (12.69)	<0.01*
East Asian	541 (1.24)	222 (1.21)	135 (1.33)	
South Asian	804 (1.85)	258 (1.41)	173 (1.70)	
Others/Unknown/mixed	10,974 (25.25)	4,751 (25.98)	1,789 (17.56)	
Deprivation score (income)				
1st quintile	2,465 (5.67)	709 (3.88)	417 (4.09)	
2nd quintile	3,308 (7.61)	1,098 (6.00)	629 (6.17)	<0.01*
3rd quintile	6,520 (15.00)	2,844 (15.55)	1,355 (13.30)	
4th quintile	14,114 (32.48)	6,130 (33.52)	3,308 (32.47)	
5th quintile	17,047 (39.23)	7,509 (41.06)	4,478 (43.96)	

[a] Subjects with demographic information

[b] Independent t-tests for continuous variables and Chi-square tests for categorical variables

* Statistical significance

Table 2. Associations between previous diagnosis received in secondary mental healthcare and stage at cancer diagnosis (N = 28,477)

	Cancer Stage at Diagnosis Number (%)			Age- and gender-adjusted	
Variables	Localized stage (n = 18,290)	Advanced stage (n = 10,187)	Unadjusted odds ratio for advanced cancer stage (95% CI)	odds ratio for advanced cancer stage (95% CI)	Fully adjusted odds ratio for advanced cancer stage [b] (95% CI)
Severe mental illness (SMI) [a]					
No	18,208 (64.22)	10,144 (35.78)	Ref	Ref	Ref
Yes	82 (65.60)	43 (34.40)	0.94 (0.65, 1.36)	1.01 (0.70, 1.47)	0.94 (0.64, 1.39)
Schizophrenia					

No	18,233 (64.24)	10,151 (35.76)	Ref	Ref	Ref
Yes	57 (61.29)	36 (38.71)	1.13 (0.75, 1.72)	1.23 (0.81, 1.88)	1.10 (0.71, 1.71)
Bipolar disorder					
No	18,266 (64.21)	10,180 (35.79)	Ref	Ref	Ref
Yes	24 (77.42)	7 (22.58)	0.52 (0.22, 1.22)	0.55 (0.24, 1.30)	0.60 (0.25, 1.42)
Schizoaffective disorder					
No	18,286 (64.22)	10,186 (357.8)	Ref	Ref	Ref
Yes	4 (80.0)	1 (20.0)	0.45 (0.05, 4.02)	0.47 (0.05, 4.38)	0.47 (0.04, 4.95)
Depression					
No	18,184 (64.22)	10,129 (35.78)	Ref	Ref	Ref
Yes	106 (64.63)	58 (36.37)	0.98 (0.71, 1.35)	0.91 (0.66, 1.26)	0.90 (0.64, 1.27)

Dementia					
No	18,229 (64.26)	10,137 (35.74)	Ref	Ref	Ref
Yes	61 (54.95)	50 (45.05)	1.47 (1.01, 2.14)*	1.00 (0.68, 1.46)	1.23 (0.82, 1.85)
Substance use disorders					
No	18,260 (64.23)	10,171 (35.77)	Ref	Ref	Ref
Yes	30 (65.22)	16 (34.78)	0.96 (0.52, 1.76)	1.01 (0.55, 1.87)	0.99 (0.52, 1.89)
Anxiety disorders					
No	18,263 (64.22)	10,173 (35.78)	Ref	Ref	Ref
Yes	27 (65.85)	14 (34.14)	0.93 (0.49, 1.78)	0.98 (0.51, 1.89)	1.15 (0.58, 2.28)
Personality disorders					
No	18,282 (64.24)	10,179 (35.76)	Ref	Ref	Ref

Yes	8 (50.00)	8 (50.00)	1.80 (0.67, 4.79)	2.15 (0.80, 5.76)	1.78 (0.65, 4.88)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Adjust for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

* Statistical significance

Table 3. Crude and adjusted relative risks for the effect of pre-existing mental disorders on general mortality among cancer patients in southeast London by Cox models (N = 43,449)

Variables	Hazard Ratio (95% Confidence Interval)		
	Age- and gender-adjusted	Model 1 [b]	Model 2 [c]
Serious Mental Illness (SMI) [a]			
No	Ref	Ref	Ref
Yes	1.53 (1.27, 1.85)*	1.71 (1.44, 2.06)*	1.74 (1.44, 2.10)*
Schizophrenia			
No	Ref	Ref	Ref
Yes	1.71 (1.38, 2.11)*	1.91 (1.55, 2.37)*	1.90 (1.54, 2.36)*
Bipolar disorder			

No	Ref	Ref	Ref
Yes	1.01 (0.66, 1.55)	1.13 (0.74, 1.73)	1.20 (0.78, 1.85)
Schizoaffective disorder			
No	Ref	Ref	Ref
Yes	3.22 (1.45, 7.17)*	2.69 (1.21, 5.98)*	2.33 (1.05, 5.20)*
Depression			
No	Ref	Ref	Ref
Yes	1.22 (1.04, 1.44)*	1.27 (1.07, 1.49)*	1.30 (1.11, 1.54)*
Dementia			
No	Ref	Ref	Ref
Yes	1.36 (1.17, 1.58)*	1.65 (1.42, 1.92)*	1.66 (1.43, 1.94)*

Substance use disorders			
No	Ref	Ref	Ref
Yes	1.24 (0.89, 1.72)	1.41 (1.02, 1.96)*	1.42 (1.02, 1.97)*
Anxiety disorders			
No	Ref	Ref	Ref
Yes	0.74 (0.50, 1.10)	0.86 (0.58, 1.30)	0.73 (0.49, 1.10)
Personality disorders			
No	Ref	Ref	Ref
Yes	1.65 (0.94, 2.91)	1.58 (0.90, 2.79)	1.50 (0.85, 2.64)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Model 1: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

[c] Model 2: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, deprivation score for income, and stage at cancer diagnosis

* Statistical significance

A Cohort Study on Mental Disorders, Stage of Cancer at Diagnosis and Subsequent Survival

Chin-Kuo Chang,[1]* Richard D Hayes,[1] Matthew TM Broadbent,[2] Matthew Hotopf,[1] Elizabeth Davies,[3] Henrik Møller,[3] Robert Stewart [1]

[1] King's College London (Institute of Psychiatry), London

[2] South London and Maudsley NHS Foundation Trust, London

[3] King's College London (Section of Cancer Epidemiology and Population Health), London

Corresponding Author: Dr. Chin-Kuo Chang, Box 92, King's College London (Institute of Psychiatry), De Crespigny Park, London SE5 8AF, United Kingdom. e-mail: chin-kuo.chang@kcl.ac.uk; TEL: +44 203 2288563; Fax: +44 203 2288551

Key words: cancer stage at diagnosis; case register linkage; severe mental illness; survival

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ABSTRACT

Background: There have been inconsistent research results reported for the effects of prior serious mental disorders on cancer mortality and morbidity.

Methods: Using the anonymised linkage between a regional monopoly secondary mental health service provider in southeast London and a population-based cancer register, a historical cohort study was constructed. Comparisons between people with and without specific psychiatric diagnosis in the same residence area for risks of advanced stage of cancer at diagnosis and general survival after cancer diagnosed were analysed using logistic and Cox models.

Results: A total of 28,477 cancer cases aged 15+ years old with stage of cancer recorded at diagnosis were identified. Among these, 2,206 subjects had been previously assessed or treated in secondary mental healthcare before their cancer diagnosis and 125 for severe mental illness (schizophrenia, schizoaffective, or bipolar disorders). No associations were found between specific mental disorder diagnoses and beyond-local spread of cancer at presentation. However, people with severe mental disorders, depression, dementia, and substance use disorders had significantly worse survival after cancer diagnosis, independent of cancer stage at diagnosis and other potential confounders.

Conclusions: Previous findings of associations between mental disorders and cancer mortality are more likely to be accounted for by differences in survival after cancer diagnosis rather than by delayed diagnosis.

Strengths and limitations of this study:

Main strengths:

- Longitudinal study design with a data linkage between two case register systems in London, UK
- Mortality information was retrieved from the national registry of death certificates in UK.

Limitations:

- The completeness rate of cancer stage was about 65%, which is within the range reported by other cancer registries in England and did not differ for most of the mental disorder groups of research interest compared to the remaining population.
- Lack of lifestyle factors (smoking, drinking, diet, obesity, and physical activities) for confounding control in survival analysis
- Small cancer case numbers of some specific mental disorders did not permit restricting the sample for sensitivity analyses. Also, size of the linked sample also did not allow further analyses of individual cancer diagnoses.

INTRODUCTION

Numerous studies have indicated a higher risk of all-cause mortality and shorter life expectancy for people with severe mental illness (SMI), including schizophrenia, bipolar disorder, schzoaffecive disorder, and sometimes depressive disorders.[1-8] The profile of causes of death among people with SMI is not substantially different from that in general population, although some specific patterns of death have been suggested, differing by sex, age group, and mental disorder diagnosis.[3 5-7 9-13] In recent decades, cardiovascular disease, stroke, respiratory diseases, suicide, and cancer have remained the leading causes.[3 5-7 9-13]

A recent population-based study revealed that men with psychiatric admissions before cancer registration had a significantly worse survival, especially for those with depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] Results from three population-based cohort studies showed significantly increased cancer mortality among people with schizophrenia for both genders,[5 9 15] but some other studies reported that it occurred in men[7 13 16 17] or women only.[18] However, other studies found no association with cancer mortality for SMI as a whole or schizophrenia specifically[7 13 16 17] and even a reduced risk was reported in one study.[6] Depression has also been found to be associated with an increase in cancer mortality.[19] Studies of the incidence of cancer in people with SMI have principally focused on schizophrenia with varying results, including reduced total cancer incidence,[18 20-25] no difference,[26-29] or increased risk.[30] A meta-analysis pooling eight studies concluded no association between schizophrenia and incidence of cancer.[27] A history of depression or alcohol-related or substance use disorders has been associated with increased cancer,[31] but inconsistent findings have been found for bipolar disorder,[32 33] dementia,[15 18 34] and null for schizoaffective disorder.[29] Evidence on the role of mental disease as a comorbidity factor in cancer is therefore still far from conclusive, but tends to indicate cancer

incidence that is either reduced or not different, and cancer mortality that is increased.[32 33]

Thinking of how to solve the puzzle shown on conflicting research results and effects of mental disorders to cancer prognosis, there are two key research questions to be answered. First, to what extent might the reduced recognition of early cancer symptoms in people with mental disorders influence the stage of cancer at diagnosis?[33 35-37] And, secondly, what is the role of mental disorders on mortality after cancer diagnosis if the issue of later presentation of cancer could be ruled out? Then, an influence of mental disorders on cancer mortality in the absence of a clear effect on underlying risk could be explained by differences in treatment access, response and adherence, as previously raised by Kisely and colleagues.[15 38] Utilising a data linkage between a large secondary mental healthcare case register in southeast London and the regional cancer registry, we sought to investigate associations between mental disorder and both disease stage at cancer diagnosis and subsequent survival.

MATERIALS AND METHODS

The South London and Maudsley NHS Foundation Trust (SLAM) Biomedical Research Centre (BRC) Case Register

The SLAM BRC Case Register was used to provide data on mental disorders for the current study. SLAM is the near-monopoly provider of comprehensive secondary mental health services for a geographic catchment consisting of four London boroughs (Southwark, Lambeth, Lewisham, and Croydon) with approximately 1.23 million residents. Clients' records for all the services provided by SLAM were electronised in 2006. In 2008, the Clinical Record Interactive Search (CRIS) system was developed as a platform for investigators to search and access full but anonymised clinical data from the fully electronic health records system in SLAM for research purposes. All people receiving

SLAM care for psychiatric assessments and / or treatment were included in the database. The demographic characteristics and clinical profiles of the Case Register population have been fully described elsewhere.[39] Ethical approval as an anonymised data resource for secondary analyses was received from Oxfordshire REC C in 2008 (reference number 08/H0606/71).

Thames Cancer Registry (TCR)

At the time of the study, TCR was the largest of eight population-based cancer registries in England, covering a population of 12 million residents in London, Kent, Surry, and Sussex. Registration was initiated by pathology reports and clinical records from hospitals and information on death certificates received from the NHS Central Register through the Office of National Statistics in 1999. When cancer is recorded as the main or contributing cause of death in the Part 1 section, the certificate is routinely sent to the regional cancer registry. Further information on demographic, clinical details, and treatments received within the first six months after cancer diagnosis was retrieved from hospitals or hospital databases by trained data collection officers. A central regional database was maintained with data added continuously and robust data quality controls. To avoid double counting, information about new tumors was cross-checked against existing registered cases. Cancer registration and cancer surveillance take place in English registries under provisions of Section 251 of the Health and Social Care Act and this permission is reviewed annually. The Thames Cancer Registry was assessed to be more than 95% complete in 2001-2007 and considered as of sufficient quality for cancer outcomes analyses.[40 41]

Anonymised process of data linkage

Data from CRIS and TCR for residents in the SLAM geographic catchment were linked using an anonymisation process by the Health Research Support Service (HRSS) Pilot Programme which was

operated by the Department of Health as part of the NHS Research Capability Programme in the UK. Memoranda of Understanding were signed between SLAM and TCR through HRSS, which in turn designed and created an infrastructure to provide a safe and confidential platform for health research. With HRSS as the "trusted third party", the linkage was performed using a series of identifiers including the NHS number and was then irreversibly de-identified, replacing the NHS number with an encrypted HRSS identification (HRSS id). The initial sample selected for analysis comprised individuals on the TCR dataset within SLAM coverage area. Thus, a retrospective cohort study of people under the care of secondary mental health services could be performed.

Covariates included

Mental disorder diagnoses were identified from two sources within CRIS: i) a primary psychiatric diagnosis (Axis 1a) categorised by ICD-10 code (a structured field, compulsory for completion by services, with a specific date in the electronic clinical records system); and ii) a supplementary natural language processing application developed using General Architecture for Text Engineering (GATE) software which extracts text strings relating to a diagnosis statement in correspondence fields. The first diagnoses from either or both sources were then categorised into the following groupings (ICD codes): dementia (F00-03), substance use disorders (F10-19), schizophrenia (F20), schizoaffective disorder (F25), bipolar disorder (F31), depressive disorders (F32-33), anxiety disorders (F40-42), and personality disorders (F60-61). Severe mental illness (SMI) was defined as a diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or bipolar disorder (F31). In the TCR data, tumor stage at presentation of cancer was routinely extracted from an individual's medical records and categorised as follows: "local" (stage 1), "extension beyond the organ of origin" (stage 2), "regional lymph node involvement" (stage 3), and "metastasis" (stage 4). Cases without sufficient information about disease stage were classified as "not known". Date of cancer diagnosis, date of

birth, sex, type of cancer, primary care trust (geographic area), and ethnic group were also routinely collected in TCR and were used as covariates. In addition, the income domain of the index of multiple deprivations in 2007 was derived on the basis of the residential postcode.[42]

Statistical analysis

All the cancer cases diagnosed in the period from 1999 to 2008 in residents of the catchment area of four London boroughs under SLAM service coverage were included in current analyses. Through the linkage performed by HRSS, any cancer detected after a contact with SLAM was marked. If multiple tumors were registered in one person, only the first cancer onset was considered. Their primary psychiatric diagnosis given in SLAM services before the cancer was identified (if any) as the major exposure of interest in current analyses. Stage of disease at cancer diagnosis was categorised into two groups: i) early stage with no spread or only local extension beyond the organ of origin (localized stage), and ii) late stages with regional lymph node involvement or metastasis (advanced stage). This was treated as a binary dependent variable and was modeled against mental disorder diagnoses by logistic regressions. Cox regression models were then assembled to estimate associations between mental disorder and survival after cancer diagnosis. The duration of follow up was defined as the period from cancer diagnosis to the date of death (any cause) or the end of the follow-up period (12 Jun, 2010), provided by TCR. Age at cancer diagnosis, gender, type of cancer, year of cancer diagnosis, primary care trust (geographic area), ethnic groups, deprivation score for income, and stage at cancer diagnosis were treated as potential confounders, where appropriate. Area-level deprivation score for income was classified into quintiles, with the 1st quintile representing the most affluent areas and applied as the reference group in modeling. Stata/IC 12.1 software for Windows (Stata Corporation, 2011) was used for all the analyses.

RESULTS

The study sample

A total of 43,746 cancer cases were identified from TCR records. Among them, 15,166 subjects (34.7%) had no information about their stage of cancer at diagnosis. No significant associations were found between psychiatric diagnosis and missing cancer stage data apart from a higher proportion of missing data in people with dementia (46.8%) compared to the remainder (35.0%). After the exclusion of people without confirmed cancer stage information and those younger than 15 years old at cancer diagnosis (n = 101), with missing date of birth (n = 1) or date of cancer diagnosis (n = 1), 28,477 cases (65.1%) remained and were included in our analyses. Among them, 55.3% were female. Up to the end of 2008, a total of 2,206 of these cancer cases had received any SLAM service (i.e. were present on the CRIS database), and 125 of these had received an SMI diagnosis prior to their cancer diagnosis.

Factors associated with extent of disease at cancer diagnosis

Of the analysed sample of cancer cases, 64.2% (n = 18,290) were diagnosed with localized stage of disease. Descriptive characteristics of the sample by stage at cancer diagnosis are presented in Table 1. Subjects with advanced stage of cancer at diagnosis were older and more likely to be male (both p values < .001), and there was significant variation by cancer type, year of diagnosis, primary care trust, and ethnic group (all p values < .001), although no clear linear trend for socio-economic deprivation was evident (details not shown).

Mental disorder and stage at cancer diagnosis

Associations between preceding mental disorders and stage at cancer diagnosis are summarised in Table 2. In summary, findings were null and there was no evidence of an association with any

diagnostic group after adjustment for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income.

Mental disorder and survival after cancer diagnosis

Associations between mental disorders and survival after cancer diagnosis are summarised in Table 3. SMI as a whole (and schizophrenia and schizoaffective disorder individually), depression, dementia, and substance use disorders were associated with worse survival after cancer diagnosis in fully adjusted models with relatively little attenuation following adjustment for stage at cancer diagnosis.

DISCUSSION

Main findings

This linkage between a population-based cancer register and a near-monopoly secondary mental health service provider with a geographic catchment of approximately 1.23 million residents provided a sufficiently large sample for this investigation. The key findings were that people who had been diagnosed with specific mental disorders in the secondary mental health service were not more likely to have cancer with advanced stage at diagnosis, but that many of the mental disorder groups had worse subsequent survival. This latter finding was significant for SMI as a whole, and for schizophrenia and schizoaffective disorder individually, as well as for those with diagnoses of depression, dementia, and substance use disorders prior to the cancer diagnosis. The stage of cancer at diagnosis in people with mental disorders did not explain their worse subsequent survival.

Advantages and limitations

The study described here benefited from the large size of the two data sources. The linkage allowed the longitudinal observation of a substantial number of cases with mental disorder diagnoses who had

subsequently developed cancer, and comparison group of the remaining people with cancer diagnoses from the same geographic catchment area. Ascertainment of vital status and deaths were achieved by linkage to death certificates provided electronically from the Office for National Statistics. Limitations include a fairly large proportion with missing data on cancer stage (34.7%). This completeness level is within the range reported by other English registries and represents the data available to the registration process. These levels have been improving with the receipt of electronic pathology data from hospitals. Importantly, the proportions with missing stage data did not differ for most of the mental disorder groups of primary interest compared to the remaining population (the only exception being dementia) and principal findings are therefore unlikely to have been biased by availability of stage information. The other issue was the lack of lifestyle factors for smoking, drinking, diet, obesity, and physical activities in our dataset, which made further confounding control inapplicable. Another limitation was that some of the required data on mental disorders were drawn from years when there was less than full information, since electronic records became comprehensive across all SLAM services during 2006; however, case numbers did not permit restricting the sample any further for sensitivity analyses. The size of the linked sample also did not permit analyses of individual cancer diagnoses. Besides, the significant finding of schizoaffective disorder for survival after cancer diagnosis in Table 3 was based on 5 cases only.

Comparisons with related studies

In the relatively scarce literature about potentially delayed cancer diagnoses among people with mental disorders, the most recent published study reported a significantly higher proportion of metastasis at cancer presentation for psychiatric patients comparing to general population (7.1% versus 6.1%) in Western Australia, especially for the cancer of breast and lung.[15] A US study, linking Surveillance, Epidemiology and End Results data to Medicare, found that people without mental

disorder were slightly more likely to have an earlier detection of colon cancer than people who had any mental disorder (53.3% versus 49.7%), although it was partially contributed by higher proportion with unknown stage when colon cancer diagnosed (6.2% versus 14.6%). The frequency of diagnosis at autopsy for colon cancer among people without mental disorder was also significantly lower than cases (1.1% versus 4.4%).[35] However, these two studies did not adjust for potential confounders in their analyses, especially for type of cancer.[15 35] Another study focusing on breast cancer with confounders adjusted found that a history of major depression was associated with a delayed diagnosis of breast cancer representing an almost ten-fold increased risk, but the opposite direction of association was found for phobia.[43] Although we should have sufficient statistical power to identify the differences, our null findings for people undergoing assessment and treatment in secondary mental health services made the issue about delayed diagnosis of cancer among people with mental illness still inconclusive. Although potential explanation about specific psychological characteristics of dispositional insensitivity to threat (if the relation really exists) was found to be associated with delayed help seeking for symptoms of rectal cancer,[36] further in-depth investigations on the effect of mental disorders to physical healthcare utilisations is needed.

On the issue of survival for people with mental disorders after cancer diagnosis, a previous study of a population-based male Swedish cohort with psychiatric admissions before cancer diagnosis by registration found significantly worse survival, especially for those who had had depressive disorders, neurotic and adjustment disorders, and alcohol-related or other substance use disorders.[14] With a similar study design, Kisley *et al.* identified a significantly elevated risk of cancer mortality for people with psychiatric disorder in Canada.[38] Advanced analyses exploring the reasons for elevated all-cause mortality following cancer diagnosis were also reported for people with known mental disorders in Western Australia, finding reduced likelihood of surgery after diagnosis of colorectal,

breast, and cervical cancers in people with mental disorders and less radiotherapy or chemotherapy receipt.[15] The US linkage between Surveillance, Epidemiology and End Results data and Medicare found that receipt of colon cancer treatment (any treatment at all stages or chemotherapy at stage 3 only) was significantly lower for people with preexisting any mental disorder, mood disorder, psychiatric disorder, and dementia.[35] Our study provided additional support to the finding that, although the stage of diagnosis for cancer of people with mental illness was not more advanced, these people were still at higher risk of death comparing to their counterparts without mental illness. The underlying reasons might differ by medical care system in countries. Further details about the treatment trajectories after cancer diagnosis for people with mental disorder are needed for advanced studies.

Implications and direction for future studies

The wider question about cancer risk and outcome in people with mental disorders has received considerable attention over the years, although studies have principally investigated overall cancer-related mortality or cancer incidence. While findings about cancer screening uptake rates among people with SMI were inconsistent across and within countries,[44] one possible reason for reasonably consistent raised cancer-related mortality in people with mental disorders but inconsistent evidence for raised cancer incidence is that the mortality is explained by delays in presentation rather than increased risk. However, we found no evidence that prior mental disorder was associated with more advanced stage of cancer at diagnosis, a measure of delay in presentation, which might because that, in UK, since 2003, GPs have been incentivised under the guide of Quality and Outcomes Framework[45] to offer regular physical health reviews to people with long-term mental health problems, including preventative cancer screening appropriate to age and gender since 2006.

Instead, consistent with other findings,[14 15 35 38] we found an association with worse survival after cancer diagnosis that was not explained by stage at presentation. This suggests that effects of mental disorder on cancer mortality primarily exert themselves after the diagnosis. Causal pathways might include reduced access to medical treatment and care, differing decisions about or tolerance of intensive regimes, and the influence of other health problems or drug effects on survival. Also, there might be differences between cancers on the impact to survival for early diagnosis, but there were insufficient data to analyze such differences among types of cancer. Clearly the components of such disadvantage require further evaluation. A greater understanding is needed of levels of utilisation of healthcare services and potential barriers to this among people with mental illness, including the extent to which this is present across individual cancer diagnoses and to which it is accounted for by the specific symptoms of the mental disorders themselves, by accompanying social disadvantage, or potentially by stigma. Also worthy of further evaluation is the potential impact that mental healthcare could have on improving physical health and other indirect influences of mental disorders on adverse health outcomes.

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COMPETING INTERESTS

The authors declare no conflict of interest in this research.

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Table 1. Descriptive statistics of cancer patients in southeast London by stage at cancer presentation from 1999 to 2008

	Number (%) / Mean ± SD			
		Subjects with stage at cancer diagnosis (N = 28,477)		
Variables	All cases (N = 43,454) [a]	Localized stage (n = 18,290)	Advanced stage (n = 10,187)	p-value [b]
Age at cancer diagnosis (yrs)	63.31 ± 17.96	60.38 ± 19.15	66.80 ± 14.29	<0.01*
Gender				
Female	~~32~~23,242 (53.49)	10,257 (56.08)	5,490 (53.89)	<0.01*
Male	20,212 (46.51)	8,033 (43.92)	4,697 (46.11)	
Type of cancer				
Lung	5,286 (12.16)	1,724 (9.43)	2,068 (20.30)	
Bladder	1,170 (2.69)	636 (3.48)	111 (1.09)	
Breast	5,943 (13.68)	2,592 (14.17)	1,833 (17.99)	
Skin	2,189 (5.04)	1,548 (8.46)	93 (0.91)	<0.01*
Prostate	4,975 (11.45)	2,657 (14.53)	634 (6.22)	
Corpus Uteri	804 (1.85)	485 (2.65)	121 (1.19)	
Colorectal	3,979 (9.16)	1,441 (7.88)	1,531 (15.03)	
Others	19,108 (43.97)	7,207 (39.40)	3,796 (37.26)	

Ethnicity				
White	26,055 (59.96)	10,766 (58.86)	6,797 (66.72)	
Black	5,080 (11.69)	2,293 (12.54)	1,293 (12.69)	
East Asian	541 (1.24)	222 (1.21)	135 (1.33)	<0.01*
South Asian	804 (1.85)	258 (1.41)	173 (1.70)	
Others/Unknown/mixed	10,974 (25.25)	4,751 (25.98)	1,789 (17.56)	
Deprivation score (income)				
1st quintile	2,465 (5.67)	709 (3.88)	417 (4.09)	
2nd quintile	3,308 (7.61)	1,098 (6.00)	629 (6.17)	
3rd quintile	6,520 (15.00)	2,844 (15.55)	1,355 (13.30)	<0.01*
4th quintile	14,114 (32.48)	6,130 (33.52)	3,308 (32.47)	
5th quintile	17,047 (39.23)	7,509 (41.06)	4,478 (43.96)	

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[a] Subjects with demographic information

[b] Independent t-tests for continuous variables and Chi-square tests for categorical variables

* Statistical significance

Table 2. Associations between previous diagnosis received in secondary mental healthcare and stage at cancer diagnosis (N = 28,477)

	Cancer Stage at Diagnosis Number (%)				
Variables	Localized stage (n = 18,290)	Advanced stage (n = 10,187)	Unadjusted odds ratio for advanced cancer stage (95% CI)	Age- and gender-adjusted odds ratio for advanced cancer stage (95% CI)	Fully adjusted odds ratio for advanced cancer stage [b] (95% CI)
Severe mental illness (SMI) [a]					
No	18,208 (64.22)	10,144 (35.78)	Ref	Ref	Ref
Yes	82 (65.60)	43 (34.40)	0.94 (0.65, 1.36)	1.01 (0.70, 1.47)	0.94 (0.64, 1.39)
Schizophrenia					

No	18,233 (64.24)	10,151 (35.76)	Ref	Ref	Ref
Yes	57 (61.29)	36 (38.71)	1.13 (0.75, 1.72)	1.23 (0.81, 1.88)	1.10 (0.71, 1.71)
Bipolar disorder					
No	18,266 (64.21)	10,180 (35.79)	Ref	Ref	Ref
Yes	24 (77.42)	7 (22.58)	0.52 (0.22, 1.22)	0.55 (0.24, 1.30)	0.60 (0.25, 1.42)
Schizoaffective disorder					
No	18,286 (64.22)	10,186 (357.8)	Ref	Ref	Ref
Yes	4 (80.0)	1 (20.0)	0.45 (0.05, 4.02)	0.47 (0.05, 4.38)	0.47 (0.04, 4.95)
Depression					
No	18,184 (64.22)	10,129 (35.78)	Ref	Ref	Ref
Yes	106 (64.63)	58 (36.37)	0.98 (0.71, 1.35)	0.91 (0.66, 1.26)	0.90 (0.64, 1.27)

Dementia					
No	18,229 (64.26)	10,137 (35.74)	Ref	Ref	Ref
Yes	61 (54.95)	50 (45.05)	1.47 (1.01, 2.14)*	1.00 (0.68, 1.46)	1.23 (0.82, 1.85)
Substance use disorders					
No	18,260 (64.23)	10,171 (35.77)	Ref	Ref	Ref
Yes	30 (65.22)	16 (34.78)	0.96 (0.52, 1.76)	1.01 (0.55, 1.87)	0.99 (0.52, 1.89)
Anxiety disorders					
No	18,263 (64.22)	10,173 (35.78)	Ref	Ref	Ref
Yes	27 (65.85)	14 (34.14)	0.93 (0.49, 1.78)	0.98 (0.51, 1.89)	1.15 (0.58, 2.28)
Personality disorders					
No	18,282 (64.24)	10,179 (35.76)	Ref	Ref	Ref

Yes	8 (50.00)	8 (50.00)	1.80 (0.67, 4.79)	2.15 (0.80, 5.76)	1.78 (0.65, 4.88)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Adjust for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

* Statistical significance

Table 3. Crude and adjusted relative risks for the effect of pre-existing mental disorders on general mortality among cancer patients in southeast London by Cox models (N = 43,449)

Variables	Hazard Ratio (95% Confidence Interval)		
	Age- and gender-adjusted	Model 1 [b]	Model 2 [c]
Serious Mental Illness (SMI) [a]			
No	Ref	Ref	Ref
Yes	1.53 (1.27, 1.85)*	1.71 (1.44, 2.06)*	1.74 (1.44, 2.10)*
Schizophrenia			
No	Ref	Ref	Ref
Yes	1.71 (1.38, 2.11)*	1.91 (1.55, 2.37)*	1.90 (1.54, 2.36)*
Bipolar disorder			

No	Ref	Ref	Ref
Yes	1.01 (0.66, 1.55)	1.13 (0.74, 1.73)	1.20 (0.78, 1.85)
Schizoaffective disorder			
No	Ref	Ref	Ref
Yes	3.22 (1.45, 7.17)*	2.69 (1.21, 5.98)*	2.33 (1.05, 5.20)*
Depression			
No	Ref	Ref	Ref
Yes	1.22 (1.04, 1.44)*	1.27 (1.07, 1.49)*	1.30 (1.11, 1.54)*
Dementia			
No	Ref	Ref	Ref
Yes	1.36 (1.17, 1.58)*	1.65 (1.42, 1.92)*	1.66 (1.43, 1.94)*

Substance use disorders			
No	Ref	Ref	Ref
Yes	1.24 (0.89, 1.72)	1.41 (1.02, 1.96)*	1.42 (1.02, 1.97)*
Anxiety disorders			
No	Ref	Ref	Ref
Yes	0.74 (0.50, 1.10)	0.86 (0.58, 1.30)	0.73 (0.49, 1.10)
Personality disorders			
No	Ref	Ref	Ref
Yes	1.65 (0.94, 2.91)	1.58 (0.90, 2.79)	1.50 (0.85, 2.64)

[a] SMI: schizophrenia, bipolar disorder, or schizoaffective disorder

[b] Model 1: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, and deprivation score for income

[c] Model 2: adjusted for age, gender, type of cancer, year of cancer diagnosis, primary care trust, ethnicity, deprivation score for income, and stage at cancer diagnosis

* Statistical significance